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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	22

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/155,452	BORTS ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application is a 371 National stage filing of PCT/GB97/00875, filed March 27, 1997, which claims benefit to provisional application 60/014,490, filed April 1, 1996.

Applicants amendment filed June 23, 2003, paper number 21, has been received and entered. Claims 1-11, 12-3 have been canceled. Claims 36-49 have been added. Claims 36-49 are pending.

Election/Restriction

Claims 36-49 are pending. The newly submitted claims have been amended from methods and processes drawn to *in vivo* practice to methods and processes practiced *in vitro*. It is noted that *in vivo* and *in vitro* methods are drawn to material different and patentably distinct methods, however the instant claims do not differ in the method steps recited from those previously set forth. Further, in the discussion of the previous claims analysis of the process of meiosis at the cellular level was set forth in the office action. Therefore, while the newly submitted *in vitro* methods are drawn to a materially different subject matter than encompassed by *in vivo* methods, because *in vitro* embodiments have been considered previously the pending claims will be considered part of the elected invention.

Claims 36-49 are currently under examination as they are directed to the elected species of animals.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 36-49 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

In the instant case, the embodiment of performing the claimed method of enabling meiotic recombination in animal cells *in vitro* is considered new matter. Initially, it is noted that support for the new claim amendments in the present specification has not been specifically pointed to in Applicants' amendment. Upon review of disclosure, no literal support for "*in vitro*"

can be found. With respect to figurative support, the working examples using yeast cells in culture could be interpreted to be in the context of *in vitro* methods. However, there are no such working examples for animal cells, and only discussion for performing the methods in animals in an *in vivo* context. Importantly, the methods of culturing and handling yeast in vitro is significantly different from the methods which would be required to culture animal cells in vitro. Even if one were to concede that culturing animal cells *in vitro* is routine, the invention as it is drawn to the unique process of fusing and culturing animal cells and subsequently causing meiosis/recombination to occur in the newly generated cell would not be considered routine. The present specification is silent with respect to any guidance for practicing the instantly claimed method with animal cells in vitro. Lacking both literal support and figurative support, the methods of using animal cells *in vitro* in the instantly claimed methods is considered new matter.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection

based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claims 36-49 stand rejected (as previously applied to claims 11, 13, 16, 17, 21-23, 30, 31 and 35) under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' note that the claimed methods have been amended from methods practiced "*in vivo*" to methods practiced "*in vitro*" and argue that the rejection is traversed to the extent that the rejection focuses on the unpredictability of the methodology to be practiced *in vivo* (page 5). Additionally, Applicants note and argue that yeast serve as a suitable model system for animal systems providing several references wherein yeast have been used as model systems (page 5). Further, it is noted and argued that yeast is often used as a model system for several art recognized reasons (page 6). Finally, Applicants note the priority date of the of the instant application and that the references used in the basis of the rejection are not prior art (bridging pages 6-7). See Applicants' amendment, pages 5-7. Applicants' arguments have been fully considered, but not found persuasive.

Examiner notes the amendments to the claims to be drawn to methods practiced *in vitro*, however the unpredictability of the claimed method is not based exclusively on practice of the

methods *in vivo*. Examiner would concede that culturing animal cells *in vitro* would be routine, however the instantly claimed methods would not use routine methods and would require new and unique method steps for fusing animal cells and forcing the newly formed cell to undergo meiosis, and based on the art of record no such methods exist for practicing the instantly claimed methods *in vitro*. The specification is silent with respect to any guidance in practicing the instantly claimed method *in vitro* with animal cells. More importantly, as set forth in the basis of the previous office action, the methods and mechanisms relied upon for practice of the claimed method do not function in animal cells as they do in yeast cells. Examiner would agree that yeast can serve as a simple model system for more complex systems present in animal cells. However as specifically set forth in the basis of the previous office action, in this case the observations made in yeast do not simply extend to the more complex meiotic system found in animal cells. Upon review of the reference provided in support of the claimed methods Examiner notes and agrees that it is recognized in the art that yeast serve as potentially useful systems for modeling more complex systems found in animal cells. However, none of the references specifically support the correlation between meiosis in yeast and animals, or that all the observations made in yeast will simply extend to more complex systems. In this case, the specification provides no specific guidance for practicing the claimed methods with animal cells and fails to provide any correlative arguments or evidence that the process of meiosis in yeast (a part of the normal life cycle in this single cell organism) would extend to animal cells, in particular to newly formed hybrid cells made by cell fusion. Moreover, the claims encompass

making cell fusions of different species of animals. To date, there is no evidence of record that such a hybrid animal cell could be made and cultured or once formed could be pushed into meiosis. The methods for manipulating and culturing yeast are well known for practicing the claimed methods to the extent they require fusing, culturing and inducing meiosis in yeast. Such methods do not exist for animal cells let alone methods for performing the methods with hybrid animal cells with uncharacterized properties and requirements. Examiner notes that the references relied upon are not "prior art" however, the teachings of the references are valid and are used to demonstrate that even to date, the instantly claimed method would require undue experimentation. Specifically, the references provide evidence that the process of meiosis functions differently in yeast and animals, in particular the presence and/or absence of mutL and mutS homologues cause different affects in yeast versus mammals. Even in the context of the specific genes contemplated in the instant disclosure< mutL and mutS homologues, the disruption of these genes in animal cells results in a non-fertile animal and a non-viable meiotic cell. It is noted that the references provide the evidence in an animal model in an *in vivo* context, however the affect of disrupting the gene is affected at a cellular level and there is no reason to doubt that what is observed *in vivo* would extend to the same cell cultured *in vitro*.

As set forth in the previous office action, enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not

'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The present invention encompasses a method of enabling meiotic recombination *in vivo* of partially homologous DNA sequences in an animal comprising: 1) genetically or physiologically manipulating cells to render defective the enzymatic mismatch repair system of said cells wherein said cells contain partially homologous DNA sequences, and 2) culturing said manipulated cells under conditions to effect meiotic recombination *in vivo*. Further, claim 22 encompasses making a hybrid animal cell wherein two populations of cells are cultured in vivo under conditions to effect meiotic recombination. The specification provides working examples of this method in yeast cells wherein the mutS and mutL genes have been inactivated by genetic alteration. The specification states "Although the specification envisages the possibility of performing such recombinations in bacteria, yeasts, plant or animal cells, in fact the experimental

data provided only demonstrate such recombinations in bacteria..." (page 3, lines 3-6). Further, the specification in review of the art only teaches miss-match repair genes from lower eukaryote, and provides no specific teaching of homologues in animals or any specific methods for isolating these gene from animal cells. Importantly, no guidance is provided in the specification teaching one of ordinary skill in the art how to employ the methodology for use in animal cells *in vivo* as demonstrated in yeast in the working examples.

Applicants argue that based on the teaching of the specification and the knowledge in the art, a skilled artisan can practice the claimed process. Further, Applicants note that references will be submitted demonstrating that one of skill in the art can practice various embodiments of the claims. See Applicants' amendment, top of page 10. Applicants' arguments have been fully considered but not found persuasive. First, it is noted that Applicants have not supplied any references demonstrating that given the guidance in the present specification one of skill in the art could practice the claimed methods *in vivo* in animals. Second, in review of the relevant art at the time of filing, it is noted that mammalian homologues of MLH1,MSH2, PMS2 genes were known. For example, Edelmann *et al.* (Cell, 1996) teach that mammalian mismatch repair genes were known, but their roles in mismatch repair in mammals were not defined (page 1125, bottom of second column). In animals *in vivo*, the process of meiosis only occurs in the germ cells and results in the halving of chromosome number during the formation of gametes. The specification provides working examples of yeast in which various mismatch repair enzymes have been rendered inactive. The specific results presented demonstrate that inactivating

mismatch repair enzymes allows the yeast to proceed through meiosis and produce viable haploid spores which subsequently can be used to form diploid cells (page 22, Table II-haploid spores and page 26, Table V-hybrid diploid cells). However, unlike in yeast, Edelmann *et al.* teach when the MLH1,MSH2, PMS2 are mutated in mice *in vivo*, each of the mice are sterile (pages 1125-1126, bridging paragraph). As specifically demonstrated in the characterization of the MLH1 knockout mice, the lack of mismatch repair gene function in mice results meiotic arrest (page 1128, second column), not meiotic recombination. Furthermore, it is noted by Edelmann *et al.* that after arrest, the cells do not progress any further indicating that hybrid cells could not be formed if they contained these alterations (page 1128, second column). Disruption of other mismatch repair genes continue to show a similar phenotype when disrupted in mice, for example, Lipkins *et al.* (Nature Genetics, 2002) teach that a disruption in the mismatch repair gene MLH3 in mice resulted in meiotic arrest. Clearly both yeast and mammals have homologs of mismatch repair genes such as the MLH1, MSH2, PMS2 genes, and these genes are involved somehow in the mismatch repair system, however, contrary to the requirement of the present methods, mutating the genes in mismatch repair in mammals results in the arrest of meiosis and not in increased recombination between non-homologous sequences.

The physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad

> enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The specification teaches that in 'eukaryote, the enzymatic mismatch repair systems are more complex than in prokaryotes' (page 3, lines 9-10). Further, it is acknowledged that 'the enzymatic mismatch repair systems involved in meiosis are to some extent different from those mitosis' and that it was 'not predictable that the techniques generally described' in the art could successfully be applied to eukaryotic cells undergoing meiosis (page 3, lines 10-14). In the instant case, at the time of filing the disruption of the yeast mismatch repair gene homologs in mammals resulted in an arrest in meiosis indicating that the methods demonstrated in yeast would not simply extend to more complex systems. As acknowledged by the specification, the art teaches that in mammalian systems the role of the mismatch repair genes becomes more complicated than that disclosed for the single cell organism such as the yeast. For example, Edelmann *et al.* teach that disruption of MLH1 resulted in sterility in both male and females, while disruption of either MSH2 and PMS2 resulted in only male sterility (page 1125, bottom of second column). Contrary to observations in yeast, Moens *et al.* (J Cell Sci, 2001)teach that the mismatch repair enzyme MLH1 'is **essential** for reciprocal recombination in the mouse' (emphasis added, page 1611, summarized in abstract). Further, the art teaches that the proteins of the mismatch repair genes in mammals appear to function in complexes and vary in function when compared to the properties of homologs in bacteria. For example, Moens *et al.* teach that

MLH1 co-localizes with MSH4, however the role of MLH1 and the role of MLH1/MSH4 is speculative (page 1620, top of second column). In another example, Santucci-Darmanin *et al.* (FASEB, 2000) more clearly demonstrate that MLH1 and MSH4 interact to form a complex during meiosis in mammals, however it is taught that other factors are likely to interact with the complex and play a functional role in meiosis *in vivo* (page 1546, middle of first column). Each Moens *et al.* and Santucci-Darmanin *et al.* demonstrate the multicomponent nature of the repair systems in mammals, and provide support for the added complexity of recombination and repair during meiosis in mammals as compared to single cell organisms. Therefore, while the present specification provides working examples that disruption of mismatch repair genes in yeast will allow recombination between non-homologous sequences of two different strains of yeast, the art teaches that the properties observed in yeast do not simply extend to higher eukaryote such as mammals. Furthermore, while mismatch repair genes from yeast and mammals appear to be homologs of each other at a structural level, the demonstration of the complex interaction of these gene products in mice compounded with the complexity of the physiology of a multicellular organism as evidenced in knock-out mice by the variability in transgene affect observed among the various known mismatch repair genes, clearly demonstrates that the observations of single cell organism such as yeast is not simply applicable to expectations in higher eukaryotic cells *in vivo*. The specification provides no guidance on how to practice the instantly claimed methods for affecting meiosis in animals *in vivo*, nor does it provide any guidance on recombining the resulting haploid cells to produce a hybrid diploid. In view of the

substantial difference and consequences of disrupting mismatch repair genes in yeast versus animals, and the lack of any guidance to practice the instantly claimed methods in animals, it would have constituted an undue burden to establish specific methodology to practice the methods as claimed.

Therefore, for the reasons above and of record, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Conclusion

No claim is allowed. The claims are free of the art of record because the art does not teach or suggest that disruption of the enzymatic mismatch repair system in animals would enable meiotic recombination.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630